Attorney Docket No. O/98414 US

REMARKS

Claims 1-4, 7-8 and 13-16 are pending in the instant application. Claims 1, 8 and 13 are independent. Claim 8 has been amended to address the question of indefiniteness. Applicants have not raised any issues of new matter.

Rejection under 35 U.S.C. §103(a)

Claims 1-4 and 7, 8 and 13-16 stand rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over Lobaccaro et al. (J. Med. Chem., 1997, 40, 2217-2227) and Napolitano et al. (J. Med. Chem., 1995, 38, 2774-2779). Applicants respectfully traverse these rejections for at least the following reasons.

The Prior Art Does Not Disclose or Suggest Selective Affinity

The Examiner has asserted that the prior art discloses the existence of the ER-α and ER-β receptors which have either agonist or antagonist affinity but does not argue that the prior art discloses or suggest the compounds which have a **selective affinity**. I.e. the question is not whether the ER-α or ER-β receptors can have either agonist or antagonist affinity, but rather whether there is an **unexpected** crossover from estrogen receptor agonist to antagonist occurring with different C-11 chain lengths at the different receptor subtypes ER-α and ER-β thereby making possible to find compounds which are ER-α agonists and ER-β antagonists. Such a discovery allows for a more selective treatment of estrogen deficiency related disorders with a lower burden of estrogen related side effects.

The prior art only discloses and suggests estrogen receptor agonists and antagonists...there is no disclosure or suggestion

with respect to mixed ER-α agonists and ER-β antagonists (and the Examiner has not asserted that there has been such a disclosure)!

Applicants respectfully point out that contrary to the arguments set forth by the Examiner, mixed ER-α agonists and ER-β antagonists simply cannot be derived from the disclosures in the prior art

As disclosed in the specification, since the ER-α and ER-β receptors have a different distribution in human tissue, the finding of compounds which possess a **selective** affinity for **either** of the two is an important technical progress making it possible to provide a more selective treatment of estrogen deficiency related disorders with a lower burden of estrogen related side-effects (Specification, page 1, lines 21 to 25).

Compounds such as disclosed and suggested in the prior art, which are either full agonists at both estrogen receptor subtypes (as we have shown with some of the prior art compounds) or full antagonists at both estrogen receptor subtypes simply would NOT achieve nor suggest this objective.

In the present invention, a specific range for the chain length at the **11β position** is claimed. Applicants assert that unexpected results show that this **specific** range identifies a series of compounds that have a specific agonist and antagonist profile, which a skilled artisan would not have known.

The Examiner is using impermissible hindsight to arrive at the assumption that one skilled in the art would be motivated by the disclosure in the prior art to extend the chain length at the **11th position**. A skilled artisan would not have had a reasonable expectation of success of achieving the selectivity of the present invention and therefore would not have been motivated to try based on the prior art disclosures.

The cited prior art fails to disclose or suggest that the crossover from estrogen receptor agonist to antagonist occurs with different C-11 chain lengths at the different receptor subtypes ER-α and ER-β making it possible to find compounds which are ER-α agonists **and** ER-β antagonists.

More particularly, neither of the cited documents allow a skilled person to learn anything about requirements for selectivity at either of the estrogen receptor subtypes. The most the skilled person can conclude is an invitation to experiment that one can achieve a change going from estrogen agonist to antagonist at higher C-11 chain lengths (from Lobaccaro et. al.). The skilled person would not conclude, nor be pointed to the fact that the possibility exists to find compounds which are agonist at one type and antagonist at the other let alone where in the chain length it is possible.

Applicants have previously presented a 37 C.F.R. §1.132 Declaration where pharmacologist Antwan Ederveen declares that the series of pharmaceutical compositions claimed within the present application are agonist at ER-α and antagonist at ER-β. In a comparison with compounds from the cited prior art, the Declarant concludes that substantially similar compounds produced different functional effects at both estrogen receptors subtypes α and β.

The Examiner has not rebutted the finding in the comparative examples and as explained by Pharmacologist Ederveen as stated in his Declaration that:

> From the results it can be concluded that all compounds (1-11) have good affinity for both estrogen receptor subtypes α and β as is evidenced by their relatively high binding affinity for *h*ER-α (Table A, column A) and *h*ER-β (Table A, column C).

> From the results it can also be concluded that **substantially similar compounds** can produce different functional effects at both estrogen receptor subtypes α and β. Thus whereas the 11-β-butenyl derivative (compound 2) behaves as an agonist on ER-α and an agonist on ER-β, the 11-β-pentenyl homologue (compound 3) behaves as an agonist on ER-α but as an antagonist on ER-β. Similarly, whereas the 11-β-butynyl derivative (compound 4) behaves as an agonist on ER-α and an agonist on ER-β, the 11-β-pentynyl derivatives (compounds 5 and 6) behave as agonists on ER-α but as antagonists on ER-β.
>
> The differential properties observed between the C4 and C5 11-β homologues, **as demonstrated in the table of results, is unexpected and does not follow in any way from the teachings of either Lobaccaro et al. or Napolitano et al.**
> (Decl. pages 4 -5)

From the arguments set forth above, as well as in the Declaration, it is evident that the Examiner is using impermissible hindsight for this invention.

In the present invention, the crossover from estrogen receptor agonist to antagonist occurs with different C-11 chain lengths at the different receptor subtypes ER-α and ER-β making it possible to find compounds which are ER-α agonists and ER-β antagonists This simply cannot follow from either of the cited documents since **the skilled person cannot learn anything about requirements for selectivity at either of the estrogen receptor subtypes from information in the prior art dealing only with estrogen agonism and antagonism.**

The Applicant maintains that the homologues demonstrate different results that are unexpected and do not follow the teachings of either Lobaccaro et al. or Napolitano et al, which only ER affinity was studied using a cytosolic ER and no reference was made to whether this is the ER-α or the ER-β receptor. For this reason alone, neither Napolitano et al. nor

Lobaccaro et al. could have suggested the presently claimed mixed profile steroids.

Unexpected pharmaceutically relevant result is significant toward overcoming a *prima facie* case of obviousness for composition claims and compound claims. A difference in antagonism or agonism at the ER-β receptor is unexpected and pharmaceutically relevant, as discussed above.

Applicants respectfully request withdrawal of the 35 U.S.C. §103(a) rejection because the declared unexpected results clearly overcome any *prima facie* case of obviousness.

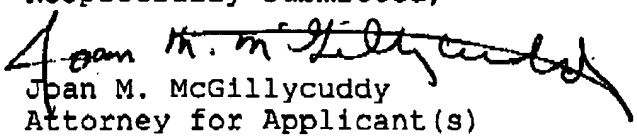
Conclusion

Based on at least the application, and the remarks herein, Applicants maintain it is not obvious in view of the cited prior art documents, either alone or in combination, to come up with the present invention.

Applicants request withdrawal of the objections and believe the present application to be in condition for allowance, which action is respectfully requested.

If the Examiner believes an interview would be helpful, especially with regard to the question of selectivity, he is invited to phone applicants' attorney at the number below.

Respectfully submitted,



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